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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/519,826	09/14/2005	Diego Walther	BB-123	3100

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EXAMINER	
CHOWDHURY, IQBAL HOSSAIN	
ART UNIT	PAPER NUMBER
1652	
MAIL DATE	DELIVERY MODE
09/17/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/519,826	WALTHER ET AL.	
	Examiner	Art Unit	
	IQBAL H. CHOWDHURY	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 June 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *25,29 and 30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *25, 29-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Application Status

Claims 25 and 29-30 are currently pending in the instant Office action.

In response to a previous Office action, a final action (mailed on 2/20/2008), Applicants filed a response and amendment received on 6/20/2008, amending claim 25, canceling claims 1-21, 24 and 28, and adding new claims 29-30 is acknowledged. Claims 22-23 and 27 remain cancelled.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 6/20/2008 has been entered.

Claims 22 and 23 are under consideration and will be examined herein.

Applicants' arguments filed on 6/20/2008 have been fully considered but are not deemed persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

New - Claim Objection

Claim 25 is objected to in the recitation "sn-TPH". The first use of a common abbreviation in a claim must be spelled out, and which may subsequently be

abbreviated. Appropriate correction is required.

Claim 29 is objected to in the recitation "polypeptide has 98% homology to SEQ ID NO: 2", which should be "polypeptide has 98% homology to the sequence of SEQ ID NO: 2". Appropriate correction is required.

Claim 30 is objected to in the recitation "polypeptide has SEQ ID NO: 2", which should be "polypeptide has the sequence of SEQ ID NO: 2". Appropriate correction is required.

Claim 25 (part a) is objected to in the recitation "SEQ ID No: 1", which should be "SEQ ID NO: 1". Appropriate correction is required.

Claim 25 (part b) is objected to in the recitation "SEQ ID No: 1", which should be "SEQ ID NO: 1". Appropriate correction is required.

Claim 25 (part c) is objected to in the recitation "SEQ ID No: 1 ------ SEQ ID No: 2", which should be "SEQ ID NO: 1 ----- SEQ ID No: 2". Appropriate correction is required.

Maintained - Claim Rejections - 35 U.S.C. § 112

Previous rejection of claim 25 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is maintained. This rejection has been discussed at length in the previous Office action. The rejection is maintained for the following reasons.

Claim 25 (part d) is directed to a combination therapeutic comprising a

polypeptide encoded by the human genomic nucleic acid sequence, which contain the gene of a human neuronal tryptophan hydroxylase (sn-TPH), and exhibit a polymorphisms due to mutation of a nucleotide at any position of the genomic DNA and an additional peripheral tryptophan hydroxylase protein for the regulation of serotonin metabolism.

Applicants argue that applicants do not need to describe the additional proteins of the combination therapeutic, i.e. peripheral tryptophan hydroxylase and providing a specific structure of that additional protein in order to satisfy the written description requirement. Applicants also argue that how the "importance" of a component of a composition affects whether the inventors had possession of that embodiment as claimed and furthermore, applicants argue that the Examiner statement regarding the "genus" of tryptophan hydroxylases is "'broad" and "structurally diverse" is not supported by any reference. Applicants further argue that the combination therapeutic as now claimed is based on the identification of a new use for the SEQ ID NO:2 protein and having knowledge of this new use, the inventors also envisioned the use of this protein with other proteins for regulating serotonin metabolism, including peripheral tryptophan hydroxylases. These other proteins are not being claimed; rather it is merely their use in combination with the protein of the subject invention that is being claimed. Tryptophan hydroxylases would be known to, and readily envisioned by, those skilled in the art having the benefit of the current disclosure. In the current case the applicants have merely referred to well-known proteins that would be readily recognized by those skilled in the art -- including the inventors. Nothing

more is necessary to establish that the inventors had "possession" of this embodiment as required by 35 U.S.C. § 112.

Applicant's arguments have been fully considered but are not deemed persuasive to overcome the rejection on written description issues. Claim 25 (d) is directed to a combination therapeutic comprising a polypeptide encoded by the human genomic nucleic acid sequence, which contain the gene of any human neuronal tryptophan hydroxylase (sn-TPH), which includes mutants and variants and exhibit any polymorphisms due to mutation of a nucleotide and an additional any peripheral tryptophan hydroxylase protein for the regulation of serotonin metabolism from any source having any structural feature, which includes mutants and variants. In particular, claim 25 still reads on a combination therapeutic comprising any human neuronal tryptophan hydroxylase (sn-TPH), which includes mutants and variants and exhibit any polymorphisms due to mutation of a nucleotide at any position of the genomic DNA and an additional any peripheral tryptophan hydroxylase protein for the regulation of serotonin metabolism from any source having any structural feature, which includes mutants and variants, which is enormously large genus of proteins and one of ordinary skill in the cannot practice the claimed invention without knowing the structure and functional relationship of the human any neuronal sn-TPH due to polymorphism and any additional peripheral TPH protein from any source used to make combination therapeutic. The specification provides no structure or sequence to the additional peripheral tryptophan hydroxylase protein. Part (D) of claim 25 also does claim the sn-TPH by a defined sequence and for which no structure is evident. The additional protein

of the combination therapeutic is a very important protein, which is similar in function of the first protein, and the combination of the two must have a specific aim and objective, which needs the fulfillment of the written description requirement, i.e. structural and functional correlation for a specific product claim. The additional protein of the therapeutic is not like pharmaceutical acceptable excipient or carrier, but an important specific protein. Regarding the mutants and variants of human neuronal sn-TPH or peripheral TPH, if a protein structure is not defined, it reads on any structure, which includes mutants and variants, for example, there are two human splice variant of TPH disclosed (Wang et al. J. Neurochemistry, 1998, see IDS), and many more mutants and variants can also exist. Therefore, a specific structural feature with recognized structure to function correlation of a claimed genus protein is necessary for fulfilling the written description requirement such that one of ordinary skilled in the art could practice the claimed invention. Claim 25 (part d) is thus drawn to a combination therapeutic comprising any human neuronal tryptophan hydroxylase (sn-TPH) derived from human genomic nucleic acid sequence, which includes mutants and variants and exhibit any polymorphisms due to mutation of a nucleotide at any position of the genomic DNA and an additional any peripheral tryptophan hydroxylase protein for the regulation of serotonin metabolism from any source having any structural feature, which includes mutants and variants, wherein said proteins structure is not fully described in the specification. No information, beyond the characterization of a protein having tryptophan hydroxylase activity in the neuronal and peripheral region. The specification does not contain any disclosure of the structure of all the mutants or variants of any peripheral

tryptophan hydroxylase used to make combination therapeutic in the claim that is required for fulfilling written description requirements. As discussed in the written description guidelines the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. A representative number of species means that the species, which are adequately described are representative of the entire genus. **Thus, when there is substantial variation within the genus, one must describe a sufficient structure and variety of species to reflect the representative structure variation within the genus.** Satisfactory disclosure of a representative structure and number depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of species disclosed. For inventions in an unpredictable art, adequate written description of a genus cannot be achieved by disclosing the structure of small portion of only one species within the genus. The genus of polypeptide having neuronal and peripheral tryptophan hydroxylase activity is structurally diverse as it broadly encompasses many mutants, and variants having different structures. As such, the disclosure solely of functional features that may or may not present in all members of the genus is insufficient to be

representative of the attributes and features of the entire genus. Therefore, the rejection is maintained.

Maintained - Claim Rejections - 35 U.S.C. § 112

Previous rejection of Claim 25 under U.S.C. 112, first paragraph, enablement requirement, is maintained. This rejection has been discussed at length in previous Office Action. The rejection is maintained for the following reasons.

The specification, while being enabling for the polypeptide of SEQ ID NO: 2 from human or a combination therapeutic of the protein of SEQ ID NO: 2 with peripheral tryptophan hydroxylase of GenBank Accession No. P17752 from human, does not reasonably provide enablement for a combination therapeutic comprising any human neuronal tryptophan hydroxylase (sn-TPH), which includes mutants and variants and exhibit any polymorphisms due to mutation of a nucleotide at any position of the genomic DNA and an additional any peripheral tryptophan hydroxylase protein from any source for the regulation of serotonin metabolism. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the claimed invention commensurate in scope with these claims.

Applicants argue that applicants have amended claim 25 to recite 95% homology to the exemplified sequence and given the high level of skill in this art, as well as the guidance provided in the applicants' specification, a person skilled in the art could readily practice the subject invention with closely-related sequences as now claimed.

Applicants' arguments have been fully considered but are not deemed persuasive to overcome the rejection on scope of enablement issues.

Claim 25 (part d) is still broad as to encompass a combination therapeutic comprising any human neuronal tryptophan hydroxylase (sn-TPH) derived from human genomic nucleic acid sequence, which includes mutants and variants and exhibit any polymorphisms due to mutation of a nucleotide at any position of the genomic DNA and an additional any peripheral tryptophan hydroxylase protein for the regulation of serotonin metabolism from any source having any structural feature, which includes mutants and variants.

The scope of the claim is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of proteins involve in serotonin metabolism, i.e. neuronal and peripheral tryptophan hydroxylase including mutants and variants broadly encompassed by the claims. However, in this case the disclosure is limited to the nucleotide and encoded amino acid sequence of only one neuronal tryptophan hydroxylase protein i.e. SEQ ID NO: 2 and one peripheral hydroxylase protein used to make the combination therapeutic.

The specification does not support the broad scope of the claims which encompass a combination therapeutic comprising any human neuronal tryptophan hydroxylase (sn-TPH) derived from human genomic nucleic acid sequence, which includes mutants and variants and exhibit any polymorphisms due to mutation of a nucleotide at any position of the genomic DNA and an additional any peripheral tryptophan hydroxylase protein for the regulation of serotonin metabolism because the

specification does **not** establish: (A) regions of the protein structure which may be modified without affecting tryptophan hydroxylase activity and; (B) the general tolerance of tryptophan hydroxylase polypeptide to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any tryptophan hydroxylase polypeptide amino acid residues with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any human neuronal TPH due to polymorphism and any additional peripheral TPH protein involve in serotonin metabolism from any source. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of a combination therapeutic any human neuronal tryptophan hydroxylase (sn-TPH) derived from human genomic nucleic acid sequence, which includes mutants and variants and exhibit any polymorphisms due to mutation of a nucleotide at any position of the genomic DNA and an additional any peripheral tryptophan hydroxylase protein having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Therefore, the rejection is maintained.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 25 and 29-30 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The nature and breadth of the claims encompass a combination therapeutic as a composition comprising neuronal sn-TPH and peripheral TPH, wherein the dictionary meaning of "therapeutic" is curative, remedial or amounting to a cure of a disease. Although the claims are not limited to specific diseases, which reads on any diseases including Alzheimer's disease, a neuronal disease, the claims, as written encompass this disease and the claims have the potential of being used to treat this diseases. Thus, references regarding these diseases are stated below which show the unpredictability of treating and preventing Alzheimer's disease and type II diabetes mellitus.

With respect to Alzheimer's disease (AD), one skilled in the art knows that the disease has no known cure. Stephenson et al. (FEBS Lett. 2005 Feb 28;579(6):1338-42. Epub 2005 Jan 28) teach that numerous studies on the molecular pathogenesis of AD implicate a wide range of factors from neurotoxic peptides (beta-amyloid) to

inflammatory processes (interleukins), where such diversity impedes the design of effective therapies for AD (see entire publication, especially p. 1338, left column, first paragraph).

While the specification teaches the behavioral change in mice having TPH-/- and TPH+/+ phenotype, which cannot be translated to use of protein of sn-TPH and peripheral TPH as therapeutic composition for curing a neuronal disease including Alzheimer's disease.

Thus, it cannot be predicted that administering the claimed polypeptides of sn-TPH and peripheral TPH can be useful in curing neuronal disease. Furthermore, the specification does not provide any *in vivo* working examples showing that the polypeptides of sn-TPH and peripheral TPH are able to treat or prevent or cure any neuronal disease, including AD in any individual.

Therefore, in view of the unpredictability in the art, the lack of *in vivo* working examples, and the lack of further guidance in how to use the claimed proteins as compositions to actually treat any neuronal diseases, including Alzheimer's disease, it would require an undue amount of experimentation to use the claimed inventions.

Withdrawn-Claim Rejections - 35 USC § 102

Previous rejection of Claims 2-3 under 35 U.S.C. 102(b) as being anticipated by Yu et al. (WO/2002/97039, publication 12/5/2002, claim priority of US application 60/294076, filed on 5/29/2001, see IDS) is withdrawn in view of cancellation of said claims.

Maintained-Claim Rejections - 35 USC § 103

Previous rejection of Claim 25 under 35 U.S.C. 103 (a) as being obvious over Yu et al. (WO/2002/97039, publication 12/5/2002, claim priority of US application 60/294076, filed on 5/29/2001, see IDS) in view of Wang et al. (J Neurochem. 1998 Oct; 71(4): 1769-72, see PTO 892) and Veenestra-VanderWeele et al. (Knockout mouse points to second form of tryptophan hydroxylase, Mol Interv. 2003 Mar; 3(2): 72-5, 50. Review, see PTO 892) is maintained and new claims 29-30 is included in this rejection. Instant claims are drawn to a combination therapeutic comprising any human neuronal tryptophan hydroxylase (sn-TPH) derived from human genomic nucleic acid sequence, and exhibit any polymorphisms due to mutation of a nucleotide at any position of the genomic DNA, and an additional any peripheral tryptophan hydroxylase protein for the regulation of serotonin metabolism.

Yu et al. teach a polypeptide of SEQ ID NO: 2 comprising 490 amino acid residues having 100% identity to SEQ ID NO: 2 of the instant application as well as nucleotide sequence (SEQ ID NO: 1), which is 100% identical to position 101-1570 of SEQ ID NO: 1 of the instant application (see sequence alignment). Yu et al. also teach that said polypeptide is human tryptophan hydroxylase having tryptophan hydroxylase activity and involved in a rate-limiting step in the biosynthesis of a number of neurologically active compounds, including serotonin (see page 2, line 1-5). Yu et al. further teach mutants of said protein and degenerate nucleic acid variants of said polynucleotide sequence (see page 5, line 21-28). Furthermore, Yu et al. teach that said polypeptide could be used as pharmaceutical composition for therapeutic treatment

related to anxiety, depression, hyperactivity or sleep disorder (see page 2, line 6-10). Yu et al. do not teach using additional peripheral tryptophan hydroxylase with neuronal tryptophan hydroxylase protein for making combination therapeutic.

Wang et al. teach two alternative splicing at the 3'-cDNA of human tryptophan hydroxylase, which give rise to two isoforms of human tryptophan hydroxylase. (see abstract). Wang et al. do not clearly teach functional significance of these two isoforms.

However, Veenestra-VanderWeele et al. teach two isoform of TPH, specifically also neuronal specific TPH2 expression in brain (see page 73, Col 2, paragraph 2). Veenestra-VanderWeele also teach by knockout inactivation of TPH1 (which is peripheral TPH) results in no serotonin production in the gut with no behavioral change but significant serotonin production in brain due to the presence of TPH2, which indicates that TPH2 (neuronal) is more potent than TPH1 in terms of serotonin metabolism (see page 73, Col 1, paragraph 2).

Since, Yu et al. clearly teach said tryptophan hydroxylase, a serotonin metabolic enzyme and a composition comprising said protein for using as therapeutic, it would have been obvious to one to ordinary skill in the art at the time of the invention was made to make a therapeutic composition comprising said neuronal tryptophan hydroxylase protein and an additional splice variant of tryptophan hydroxylase of Wang et al. and Veneestra-VanderWheele et al. for increased serotonin production.

One of ordinary skill in the art would have been motivated in making a therapeutic composition comprising the polypeptide of Yu et al. and adding another splice variant of tryptophan hydroxylase protein (non-neuronal, i.e. peripheral) of Wang

et al., which has the same activity, and thereby enhance the serotonin production for treating disease related to anxiety, depression, hyperactivity or sleep disorder.

One of ordinary skill in the art would have a reasonable expectation of success because Yu et al. suggested to make a composition comprising said protein could be used for therapeutic purpose.

Applicants argue that WO 2002/97039 merely discloses proteins that "share structural similarity with animal hydroxylases, and particularly tryptophan hydroxylases, which are involved in a rate-limiting step in the biosynthesis of a number of neurologically active compounds, including, but not limited to, DOPA, serotonin and melatonin" (page 2, lines 1 - 5). WO 2002/97039 does not disclose any biological data verifying the function of the proteins. More importantly, in addition, it is nowhere stated that the polypeptide depicted in SEQ ID No. 2 functions as a neuronal tryptophan hydroxylase (snTPH). The present application teaches that serotonin is independently synthesized by two different tryptophan hydroxylase isoenzymes in the peripheral tissues and in the neurons. The inventors of the present invention have succeeded in providing nucleic acid molecules encoding a protein with the enzymatic activity of a neuronal tryptophan hydroxylase (snTPH). In contrast, the protein of WO 2002/97039 is only *assumed* to have a general tryptophan hydroxylase activity, wherein there is no distinction between peripheral and neuronal tryptophan hydroxylase activity. Thus, WO 2002/97039 fails to disclose or even suggest that SEQ ID No.2 is a specifically neuronal isoform of tryptophan hydroxylase. Without this knowledge there would be no reason to propose the combination therapeutic

composition as set forth in claim 25. It is well established in the patent law that the mere fact that the purported prior art could have been modified or applied in some manner to yield an applicant's invention does not make the modification or application obvious unless "there was an apparent reason to combine the known elements in the fashion claimed" by the applicant. *KSR International Co. v. Teleflex Inc.*, 550 U.S. (2007). Furthermore, an applicant's invention is not "proved obvious merely by demonstrating that each of its elements was, independently, known in the (purported) prior art." The secondary references cited in support of this obviousness rejection do not cure or even address the aforementioned deficiencies of the primary reference. Specifically these references do not disclose or suggest that SEQ ID NO: 2 is a neuronal tryptophan hydroxylase. Without this knowledge there would be no reason to produce the combination therapeutic now claimed. An assertion of obviousness without the required suggestion or expectation of success in the prior art is tantamount to using the applicant's disclosure to reconstruct the prior art to arrive at the subject invention. Hindsight reconstruction of the prior art cannot support a § 103 rejection, as was specifically recognized by the CCPA in *In re Sponnoble*, 56 CCPA 823, 160 USPQ 237,243 (1969). The cited references, either alone or in combination, do not provide a suggestion of the claimed invention and, certainly, no expectation of success.

Applicants arguments have been fully considered but are not persuasive because Yu et al. indeed teach a tryptophan hydroxylase protein from human, which is 100% identical to SEQ ID NO: 2 of the instant application and further suggest that said protein is a tryptophan hydroxylase based on the structural similarity (page 2, line 1-5),

and a composition comprising said protein. The function and identifying characteristics of a protein are the inherent properties of a protein and there is explicit suggestion that said protein is tryptophan hydroxylase and involved in serotonin metabolism. The claim does not require biological data but the protein, which is taught by Yu et al. There is no deficiency of Yu et al. reference as discussed above because the product (protein) of the reference and the product (protein) of the instant application is the same. In addition, Instant claims are product claims i.e. a tryptophan hydroxylase, and not methods of use, and thus the intended use of disclosed product is irrelevant. Besides, **Supreme Court** decision on *KSR Int'l v. Teleflex, Inc.* further strengthen the TSM test (teaching, suggestion and motivation) to combine the prior art elements to meet the claimed subject matter (see KSR Int'l Co. V. Teleflex, Inc., No 04-1350, US Apr. 30, 2007). Therefore, the rejection is maintained as discussed. The cited references teach all the limitation of claimed invention as well as a successful method for producing a secretory form of protein and one of ordinary skill in the art would be motivated to combine the teachings of the references to arrive the claimed invention (see KSR Int'l Co. V. Teleflex, Inc., No 04-1350, US Apr. 30, 2007).

As discussed previously, Since, Yu et al. clearly teach said tryptophan hydroxylase (which is 100% identical to SEQ ID NO: 2 of the instant application), a serotonin metabolic enzyme and a composition comprising said protein for using as therapeutic, it would have been obvious to one to ordinary skill in the art at the time of the invention was made to make a therapeutic composition comprising said neuronal tryptophan hydroxylase protein and an additional splice variant of tryptophan

hydroxylase of Wang et al. and Veneestra-VanderWheele et al. for increased serotonin production.

One of ordinary skill in the art would have been motivated in making a therapeutic composition comprising the polypeptide of Yu et al. and adding another splice variant of tryptophan hydroxylase protein of Wang et al. to enhance the serotonin production for treating disease related to anxiety, depression, hyperactivity or sleep disorder.

One of ordinary skill in the art would have a reasonable expectation of success because Yu et al. suggested to make a composition comprising said protein could be used for therapeutic purpose.

Therefore, the rejection is maintained as discussed.

Conclusion

Claims 25 and 29-30 are pending.

Claims 25 and 29-30 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Iqbal Chowdhury, Ph.D. whose telephone number is 571-272-8137. The examiner can normally be reached on 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Nashaat T. Nashed can be reached on 703-272-0928. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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